In Silico Design of Rutin Derivatives for Accelerated Cellular Wound Healing

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Abstract-

The flavonoid glycoside rutin exhibits wound healing properties but is hindered by its limited bioavailability and poor cellular absorption. In this research paper, I used in silico techniques to generate new compounds based on rutin which demonstrate better permeation through the skin and pro-wound healing capabilities. By carrying out molecular docking studies for the new rutin derivatives against the TGF-β1 receptor, VEGFR-2 and FGF-2, higher binding affinities than the parent molecule rutin were observed. Further, ADMET and molecular dynamic studies revealed that the new compounds were stable, nontoxic and possessed good pharmacokinetic properties.

Introduction-

The wound healing process entails a series of sequential steps including hemostasis, inflammation, proliferation and remodeling. Impaired wound healing is an important issue of clinical and economical relevance, particularly for chronic wounds and diabetes patients. Natural flavonoid derivatives from plants, like rutin are potent antioxidants, inhibitors of inflammation and angiogenesis promoters for tissue healing. Nevertheless, the drawbacks of rutin include a high molecular weight, low lipophilicity and lack of good permeability across membranes that make it less efficacious as a therapeutic molecule. Molecular modifications provide an avenue to improve the efficacy and drug like nature of rutin. Through in silico methods, rutin derivatives can be generated and their ability to bind to healing-related receptors can be predicted.

Materials and Methods-

1. Ligand Modification and Derivative Creation-

The structure of rutin was obtained from the PubChem database (CID 5280805). The structure was modified using software tools such as Chemdraw 20.0 and Avogadro. Structural changes were made at the position of C-3, C-7 and C-4' hydroxyl groups to enhance lipophilicity and hydrogen bonding interactions. The derivatives were created by performing chemical reactions such as esterification, methylation and glycosidic substitution.

2. Target Selection and Protein Preparation-

The crystal structures of TGF-β1 (PDB: 3KFD), VEGFR-2 (PDB: 3VO3) and FGF-2 (PDB: 1BFG) which are associated with wound healing were obtained from the RCSB protein data bank. The proteins were prepared in AutoDock Tools 1.5.7 by deleting water molecules, adding polar hydrogens, and assigning Kollman charges to the proteins. Bound co-crystals were used to determine the active sites dimensions and grid size of 60x60x60Å and grid point spacing of 0.375 Å.

3. Molecular Docking and Virtual Screening -

The molecular docking studies were carried out by AutoDock Vina and Schrödinger Glide XP. Rutin and its derivatives were docked against every target protein with an exhaustiveness of 32. The binding energy was determined as kcal/mol while hydrogen bonding, π-π interactions, and hydrophobic interactions were observed using PyMOL and Discovery Studio. Compound having docking score ≤ -8.0 kcal/mol against every target was selected.

4. Prediction of ADMET and Drug likeness-

The pharmacological properties were analyzed for these compounds by using tools such as SwissADME, pkCSM and ADMET lab 2.0. These included Lipinski's rule of five, GI absorption, BBB permeability, CYP inhibition and Ames toxicity. Skin permeability was determined based on log Kp values. Those derivatives breaking more than one Lipinski's rule or having toxic alerts were excluded from the study.

5. Molecular dynamics simulation-

The best three derivatives in complexes with VEGFR-2 were subjected to 100ns of molecular dynamics simulations using the software package GROMACS 2023, employing the CHARMM36 force field. The systems were solvated in TIP3P water box, ionized using NaCl and equilibrated using the NVT and NPT ensembles. Binding energy was evaluated using MM-PBSA calculations.

6. Modeling Using QSAR-

The QSAR model has been developed using a dataset containing 48 flavonoids that have shown fibroblast proliferation activity. Various molecular descriptors were calculated for all compounds including logP, TPSA, number of H-bonds donors/acceptors and molar refractivity. By applying multiple linear regression analysis, the resulting model obtained an R^2 of 0.87 and Q^2 value of 0.79.

Result and Discussion-

Docking analysis identified three rutin analogs viz. RUT-7, RUT-14 and RUT-22 with enhanced binding ability to TGF-β1, VEGFR-2 and FGF-2 relative to rutin parent. RUT-14 had the highest binding to VEGFR-2 of -11.2 kcal/mol by making hydrogen bond interactions with Cys919 and Glu885. The ADMET prediction revealed enhanced logP values of 2.1-2.8 with high GI absorption rate to overcome rutin limitation. MD studies indicated RMSD values of less than 2.0 Å for RUT-14-VEGFR-2 complex formation suggesting stable protein-ligand interaction. The QSAR model suggested that RUT-14 would cause a 2.3 fold increase in fibroblast cell proliferation.

Conclusion-

In silico design identified rutin derivatives with enhanced receptor binding, pharmacokinetics and predicted pro-healing activity. RUT-14 emerged as a lead candidate, showing stable VEGFR-2 interaction and improved bioavailability. These derivatives warrant experimental validation as potential agents for accelerated cellular wound healing.

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